EXHIBIT

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the Fiscal Year Ended December 31, 2002

or

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission file number 000-19319

Vertex Pharmaceuticals Incorporated

(Exact name of registrant as specified in its charter)

Massachusetts (State of incorporation)	**04-3039129** (I.R.S. Employer Identification No.)
130 Waverly Street Cambridge, Massachusetts (Address of principal executive offices)	**02139-4242** (Zip Code)

(617) 444-6100
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Exchange Act: None

Securities registered pursuant to Section 12(g) of the Exchange Act:
Common Stock, $0.01 Par Value Per Share
(Title of class)

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes [X] No [ ]

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. [X]

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12b-2 of the Act). Yes [X] No [ ]

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) based on the last reported sale price of the Common Stock on The Nasdaq Stock Market on June 28, 2002, was $893,950,000.

As of March 26, 2003, the registrant had 76,502,161 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive Proxy Statement for the 2003 Annual Meeting of Stockholders to be held on May 21, 2003 are incorporated by reference into Part III.

that GlaxoSmithKline had begun Phase I evaluation of VX-385. We expect that GlaxoSmithKline will continue clinical development of this compound in 2003. VX-385 is the third drug candidate that GlaxoSmithKline and Vertex have advanced into development as part of an ongoing collaboration to develop and commercialize HIV protease inhibitors. VX-385 is chemically distinct from Agenerase, 908, and other currently marketed protease inhibitors.

Background: Treatment of HIV/AIDS

Infection with HIV leads to AIDS, a severe, life-threatening impairment of the immune system. The World Health Organization (WHO) estimates that approximately 36.1 million individuals worldwide are infected with HIV. The U.S. Centers for Disease Control estimates that there are 980,000 patients in the United States infected with HIV.

Protease inhibitors (PIs) are used as part of combination regimens for the treatment of HIV. PIs block the cleavage of HIV polyproteins into active proteins, and result in the production of non-infectious viral particles. Currently, more than 174,000 of the HIV patients receiving drug treatment in the U.S. take at least one PI. The market for HIV PIs is highly competitive, with seven different PIs vying for a share of the market. Worldwide sales of HIV PIs were estimated at more than $1.6 billion in 2002, and U.S. sales alone were estimated at more than $950 million in 2002.

There are now four classes of antiviral drugs approved for the treatment of HIV infection and AIDS: nucleoside reverse transcriptase inhibitors (NRTIs), such as AZT and 3TC; non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as efavirenz; the fusion inhibitor enfuvirtide; and PIs, including Agenerase.

Sepsis (Serono; Taisho)

In 2001, Vertex advanced VX-799, a small molecule caspase inhibitor, into preclinical development targeting the treatment of sepsis. Sepsis is a life-threatening bacterial infection of the bloodstream that overwhelms the body's immune system and most commonly occurs among patients who have underlying conditions such as trauma, surgery, burns, cancer and pneumonia. Caspases play integral roles in both programmed cell death and inflammation, which have been implicated in sepsis. Sepsis may progress to multi-organ failure, shock and death. A potent caspase inhibitor may have the potential to provide a powerful treatment option for sepsis patients. Sepsis affects approximately 700,000 individuals in the U.S. each year and an additional 1.2 million in Europe and Japan. Sepsis results in an estimated 200,000 deaths each year.

Vertex is currently conducting a range of preclinical studies with VX-799. Under an agreement signed in 2000, Serono S.A. holds an option to develop and commercialize VX-799 in Europe and as part of a joint venture with Vertex in the U.S. Taisho holds the option to develop and commercialize VX-799 in Japan and certain Asian markets.

Background: Caspases and Sepsis

Caspases are a family of 11 enzymes that play roles in numerous biological processes, including programmed cell death (apoptosis) and inflammation. More information on caspases is available in the section titled "Caspase Program" on page 15. VX-799 has produced encouraging results in an apoptosis-dependent model of organ failure and several models of bacterial-induced sepsis. VX-799 may also have the potential to treat other diseases in which increased caspase activity is implicated.

Inflammation and Autoimmune Disease

Inflammatory Disease

*Interleukin-1*β Converting Enzyme Program (Aventis)

We are conducting research and development on inhibitors of interleukin-1β converting enzyme (ICE; caspase-1) for the treatment of acute and chronic inflammatory conditions. We are collaborating with Aventis S.A. in the development of the lead ICE inhibitor compound, pralnacasan (VX-740), and Aventis is investing to develop pralnacasan in parallel for both rheumatoid arthritis and osteoarthritis. In January 2003, Aventis began a Phase II proof-of-concept study of pralnacasan in patients with osteoarthritis. The study will evaluate 400 patients treated with pralnacasan or placebo for 12 weeks. The study is intended to enable Vertex and Aventis to evaluate the safety and efficacy of pralnacasan in osteoarthritis patients. We expect that Aventis will begin a Phase IIb study of pralnacasan in patients with rheumatoid arthritis in the second quarter of 2003.

In 2002, Aventis completed a 250 patient Phase IIa study in rheumatoid arthritis to evaluate clinical activity using standard measures of response to treatment, including the American College of Rheumatology (ACR) response criteria, which measure improvement in patient- and professionally-reported disease severity and activity. Data from the Phase IIa clinical trial demonstrated that treatment with pralnacasan was well tolerated and led to positive anti-inflammatory effects in patients with rheumatoid arthritis. More specifically, the Phase IIa data demonstrated that:

- Patients receiving pralnacasan exhibited a dose-dependent trend towards improvement in signs and symptoms of disease as measured by ACR20 response rates after 12 weeks.
- Patients receiving 1200 mg/day of pralnacasan in the intention-to-treat population exhibited ACR20 response rates of 44% compared to a response rate of 32.7% in the group receiving placebo.
- In post-hoc subset analyses, both patients receiving stable concomitant methotrexate (MTX) treatment for >6 months and patients not receiving concomitant MTX treatment exhibited statistically significant, dose-dependent improvement in ACR20 response rates with pralnacasan treatment.
- Patients receiving the higher dose of pralnacasan (1200 mg/day) had statistically significant reductions in the inflammatory biomarkers C-reactive protein, erythrocyte sedimentation rate, and serum amyloid A.
- Treatment with pralnacasan enabled patients to reduce their concomitant corticosteroid therapy.
- Pralnacasan was well tolerated. The incidence of dose limiting adverse events (AEs) were similarly distributed among treatment groups overall. The most common AEs judged to be treatment-related were mild to moderate diarrhea and nausea, which were seen in <5% of the study population and were generally unrelated to dose.

In 2000, Aventis completed a Phase IIa 28-day clinical trial of pralnacasan in patients with rheumatoid arthritis to evaluate the safety and pharmacokinetics of multiple doses of pralnacasan. Results showed dose-dependent suppression of the production of interleukin-1β‴ a cytokine that plays a role in inflammation and tissue damage. A Phase I clinical trial of the compound, completed by Aventis in 1999, showed that the compound was well-tolerated in humans in a range of single doses. Under our 1999 agreement, Aventis holds an exclusive worldwide license to develop, manufacture and market pralnacasan in any indication, as well as an exclusive option for certain other compounds discovered under our previous research collaboration with Aventis. We will receive milestone payments for successful development of pralnacasan in rheumatoid arthritis, as well as for each additional indication for which it is developed (including osteoarthritis). Additionally, we will receive royalties on any sales of pralnacasan and Aventis will partially fund a Vertex co-promotion effort in the U.S.

Background: ICE Inhibitors for Inflammatory Disease

ICE (caspase-1) is an enzyme that controls the release of active interleukin-1 beta (IL-1β) (one of two forms of IL-1) and IL-18 from white blood cells into the bloodstream and within tissues. IL-1β and IL-18 are cytokines that mediate a wide range of immune and inflammatory responses in many cell types. Early in the inflammatory process, IL-1β is released from white blood cells, initiating a complex cascade of events that results in inflammation and tissue damage. IL-18 is an important factor in the activation of lymphocytes, a type of white blood cell. Elevation of IL-1β and IL-18 levels has been correlated with disease states in a number of acute and chronic inflammatory diseases.

Rheumatoid arthritis (RA) is the lead indication for the pralnacasan development program. In patients with RA, increased activity of IL-1β and IL-18 is observed in joint tissues during disease flare-ups, and IL-1β and IL-18 are known to activate osteoclasts, a cell type important in bone erosion characteristic of rheumatoid arthritis.

There are more than 6 million patients with RA worldwide, including approximately 2.1 million in the United States. The main drugs currently used to treat RA are non-steroidal anti-inflammatory drugs (NSAIDs) such as Motrin (ibuprofen) and Celebrex (celecoxib). These drugs are palliative—they relieve pain and swelling but do not reverse or prevent the progression of the disease. Methotrexate is a disease-modifying drug that is widely used, but its use is associated with side effects that include liver toxicity. Even when tolerated well, over the long term many patients become unresponsive to methotrexate. Newer therapies including Enbrel® (etanercept) and Remicade® (infliximab) provide a strong rationale for a new kind of disease-modifying therapy that involves inhibition of the cytokine tumor necrosis factor (TNF) alpha. In 2001 Kineret® (anakinra) became the first therapy approved for RA targeting the cytokine IL-1β. However, these newer agents are injectable, and can be inconvenient and painful to administer. We believe that a well tolerated oral cytokine inhibitor such as pralnacasan may have significant commercial advantages.

Osteoarthritis (OA) is the second indication for which pralnacasan is being developed. The inflammatory response plays a large role in the joint damage characteristic of OA, and increased cytokine activity has been observed in OA. Specifically, IL-1β is a key driver of pathology in OA, and animal models provide a strong rationale for pursuing IL-1β modulation for the treatment of OA.

OA, a degenerative joint disease, is the most common form of arthritis, afflicting more than 240 million patients worldwide, including more than 21 million in the United States alone. Onset generally occurs after middle age, and as the disease progresses, it causes the loss of cartilage, damage to bone, formation of bone spurs, and inflammation of the soft tissues. OA may also occur in joints that have suffered previous injury, have been subjected to prolonged heavy use, or have been damaged by prior infection or inflammatory arthritis. Patients with OA experience pain, tenderness, swelling and progressive loss of mobility. OA is currently treated with over-the-counter drugs as well as palliative treatment such as NSAIDS and COX-2 inhibitors. These drugs do not address the underlying progressive joint destruction, while patients with more severe cases may become candidates for partial or total joint replacement surgery.

Vertex and Aventis scientists began collaborating in 1993 to discover and develop orally available inhibitors of ICE. Our design efforts were based on the three-dimensional atomic structure of ICE, which was solved by Vertex researchers in 1994. As the result of an extensive, jointly conducted synthesis and research program, pralnacasan was selected as a development candidate in 1997. We believe that pralnacasan is the only specific ICE inhibitor to be advanced into clinical trials and is the most advanced oral cytokine inhibitor in development.